Remarks

Claims 18, 19, 21-26, 30, 31, and 33-43 were pending in the subject application. Claims 40-43 have been withdrawn. By this Amendment, claims 23, 35, and 39 have been amended, claim 19 has been cancelled, and new claims 44-47 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with or acquiescence in the Examiner's position. Accordingly, claims 18, 21-26, 30, 31, and 33-47 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 for the subject application. Also submitted herewith is an Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicants respectfully request that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

By this Amendment, claims 45-47 have been added. Support for claims 45-47 can be found, for example, at page 16, lines 1-7; page 18, lines 1-3; and Examples 1 and 2 at pages 18-20 of the specification as originally filed.

Claim 23 has been objected to under 37 C.F.R. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. By this Amendment, the applicants have amended claim 23 to depend from claim 18, instead of claim 21. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 19 and 33 are objected to under 37 C.F.R. §1.75(c), as being substantial duplicates. The applicants respectfully submit that claim 33 is not a substantial duplicate of claim 19. However, by this Amendment, the applicants have cancelled claim 19 to expedite prosecution of the subject application. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claim 35 has been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully submit that the claimed subject matter is enabled

by the specification. However, by this Amendment, the applicants have amended claim 35 to recite that the neuronal cells of the one or more aggregates are living cells that remain viable *in vivo* upon implantation. Support for this amendment can be found at page 8, lines 9-14; page 9, lines 1-6; and Example 2 at page 20 of the specification. Claim 35 no longer recites the phrase "having not begun to degenerate". The specification teaches those of ordinary skill in the art how to make and use the recited cell culture without resort to undue experimentation. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claim 39 has been rejected under 35 U.S.C. §112, second paragraph, as indefinite. The applicants respectfully submit that the claim is not indefinite. However, by this Amendment, the applicants have amended claim 39 to recite that the cells are "supported by" the plate. As indicated at page 17, lines 24-27, of the specification, cells can be supported by the plate while suspended in culture media. The applicants respectfully submit that the claim conveys the scope of the claimed subject matter to those skilled in the art. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 18, 19, 22-26, and 33 have been rejected under 35 U.S.C. §102(a) as being anticipated by Andrews *et al.* (poster presentation from Cell Culture and Engineering Conference in Snowmass, CO, 2002). The applicants respectfully traverse.

At page 13, the Office Action indicates that because T. Freeman, C. Arriagada, and J. Rivera are inventors on the subject application, but are not listed as authors on the Andrews *et al.* presentation, the Declaration under 37 C.F.R. §1.132 by Dr. Caviedes, which was submitted with the applicants' previous response, is insufficient to overcome the rejection. The applicants respectfully disagree and submit that the Examiner's analysis is incomplete. The applicants agree that "by another" in §102(a) refers to those situations in which the authorship differs in any way from the inventive entity, *i.e.*, where the authors are not identical to the inventors. However, it is exactly this situation, where there is overlap between the inventors of the patent application and the authors of the cited reference, in which a Declaration under 37 C.F.R. §1.132 may be submitted by one of the inventors to show that the cited reference represents the inventors' own work, in order to overcome the rejection. In fact, if the authorship of the cited reference was identical to the inventive entity, no Declaration would be required. As stated by MPEP §715.01(c), "unless it is a statutory bar, a

rejection based on a publication may be overcome by a showing that it was published either by applicant himself/herself or on his/her behalf." As explained further in this section of the MPEP:

> Where the applicant is one of the co-authors of a publication cited against his or her application, he or she may overcome the rejection by filing an affidavit or declaration under 37 C.F.R. 1.131. Alternatively, the applicant may overcome the rejection by filing a specific affidavit or declaration under 37 C.F.R. 1.132 establishing that the article is describing applicant's own work. An affidavit or declaration by applicant alone indicating that applicant is the sole inventor and that the others were merely working under his or her direction is sufficient to remove the publication as a reference under 35 U.S.C. 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). (emphasis added)

The sufficiency of a Declaration under 37 C.F.R. §1.132 in the present situation is reiterated in MPEP §2132.01, as well:

> Applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982) (discussed below). Therefore, where the applicant is one of the co-authors of a publication cited against his or her application, the publication may be removed as a reference by the filing of affidavits made out by the other authors establishing that the relevant portions of the publication originated with, or were obtained from, applicant. Such affidavits are called disclaiming affidavits. *Ex parte Hirschler*, 110 USPQ 384 (Bd. App. 1952). The rejection can also be overcome by submission of a specific declaration by the applicant establishing that the article is describing applicant's own work. *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). (emphasis added)

These declarations or affidavits are commonly referred to as "Katz declarations" after *In re Katz*, where the court held that authorship of a publication does not give rise to any presumption with respect to inventorship. An uncontradicted "unequivocal statement" from the applicant regarding the subject matter disclosed in an article, patent, or published application will be accepted as establishing inventorship. *In re DeBaun*, 687 F.2d 459, 463, 214 USPQ 933, 936 (CCPA 1982); MPEP §716.10.

The Declaration under 37 C.F.R. §1.132 by Dr. Caviedes, which was submitted with the applicants' previous response, is sufficient to show that the Andrews *et al.* presentation represents the inventors' own disclosure published less than one year prior to the effective filing date of the subject application. "[O]ne's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar." *In re Facius,* 161 USPQ 294, 301 (CCPA 1969); and MPEP §715.01(c). Therefore, under the authority of *In re Facius*, the disclosure contained in the

Andrews *et al.* presentation cannot be used as a prior art reference against the applicants' claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(a) is respectfully requested.

Claims 18, 21-26, 30, 31, and 35-39 have been rejected under 35 U.S.C. §103(a) as being obvious over Takazawa *et al.* (U.S. Patent No. 5,219,752) in view of Studer *et al.* (Published International Application No. WO 00/05343) and further in view of Boss *et al.* (U.S. Patent No. 5,411,883). The applicants respectfully traverse.

The cell culture of the invention would not have been obvious to a person of ordinary skill in the art at the time the invention was made, based on the references cited in the Office Action. Submitted herewith for the Examiner's consideration is a Declaration under 37 C.F.R. §1.132 by Dr. Pablo Caviedes, including Exhibits A-C.

The teachings of the cited references do not provide a reasonable expectation of success. Claims 18 and 39 of the subject application recite that the cell culture comprises process-forming neuronal cells of the central nervous system and has a calcium concentration of 100 μM or less. The empirical data in columns 17-22 of the Takizawa *et al.* patent indicate that the aggregation of fetal kidney cells essentially occurs when a threshold calcium concentration is reached. In contrast, the inventors of the subject invention have found that process-forming neuronal cells of the central nervous system will aggregate when cultured at a calcium concentration of 100 μM or less. The Takazawa *et al.* patent proposes that various adherent animal cells can be cultured using the method disclosed therein, including the 500+ cells tabulated in columns 5-12. These cells represent a very diverse variety of tissues, *e.g.*, bat lung cells, goldfish fin cells, goose sternum cells, human bone marrow cells, human breast cells, human pancreatic cells, mosquito larval cells, moth ovarian cells, snail embryonic cells, viper spleen cells, *etc.* However, the only cells described in the Takazawa *et al.* patent as actually being cultured with the disclosed method are kidney cells, *i.e.*, 293 cells (human fetal kidney) and BHK 229 cells (hamster kidney). In the Declaration, Dr. Caviedes indicates,

> absent supporting empirical data, such as that provided in the subject application, one of ordinary skill in the art would not have a reasonable expectation of success in creating a cell culture comprising neuronal cells of the CNS that cluster into aggregates, as recited in claims 18 and 39.

Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The Takazawa *et al.* patent only provides a reasonable expectation of success in culturing kidney cells as described, not neuronal cells, and certainly not neuronal cells of the central nervous system that cluster into aggregates, as recited in the claims of the subject application.

Furthermore, assuming *arguendo* that the references cited in the Office Action support a reasonable expectation of success in producing the cell culture of the invention, the results obtained using neuronal cells of the cell culture of the invention were significantly better than could have been expected, as shown by Exhibits B and C, which accompany Dr. Caviedes' Declaration. When suspensions of the RCSN-3 cell line (a rat substantia nigra cell line) were implanted into the striatum of rats previously lesioned in the nigrostriatal pathway with 6-hydroxydopamine (6-OHDA). This toxin-induced animal model is well known in the art and accepted for simulating the motor deficits occurring in Parkinson's disease, and considered appropriate for experiments on morphological and behavioral recovery after partial lesioning of the nigrostriatal DA system (Iancu R. *et al.*, *Behavioral Brain Research*, 2005, 162:1-10; Nishimura, F. *et al.*, *Stem Cells*, 2003, 21:171-180; Bjorklund L.M. *et al.*, *PNAS*, 2002, 99(4):2344-2349; Shingo T. *et al.*, *Journal of Neuroscience Research*, 2002, 69:946-954; Mukhida K. *et al.*, *Journal of Neuroscience*, 2001, 21(10):3521-3530; Sawamoto K. *et al.*, *PNAS*, 2001, 98(11):6423-6428; Dabben-Sali F. *et al.*, *FASEB J.*, 2001, 15:164-170; Dunah A.W. *et al.*, *Molecular Pharmacology*, 2000, 57:342-352; Bilang-Bleuel A. *et al.*, *PNAS USA*, 1997, 94:8818-8823). Exhibit B is a book chapter entitled "An Immortalized Neuronal Cell Line Derived from the Substantia Nigra of an Adult Rat: Application to Cell Transplant Therapy" (In: "Parkinson's Disease", E. Ronken & G. van Scharrenburg, editors, IOS Press, Amsterdam, Netherlands, 2002, pages 120-132), which describes the implantation of the RCSN-3 cell line using conventional culture methods. As indicated in Example 1, at page 18, lines 27-30, and page 19, lines 1-5, of the subject application, and page 3 of Exhibit B (Materials and Methods—Cell Culture), the RCSN-3 cell line was established from a primary culture of the striatum of Fisher 344 rats, and exposed to media conditioned with the UCHT1 cell line (Caviedes R. and Stanbury J.B., *Endocrinology*, 1976, 99:549-554). RCSN-3 cells retain the morphology of the neuronal phenotype (Cardenas A.M. *et al.*, *Neuroreport*, 1999, 10(2):363-369). Exhibit C is a graph showing results

from implantation of the RCSN-3 cell line following culture in the cell culture of the invention. Gradual behavioral recovery (reduction of apomorphine-induced rotation scores) was observed in transplanted animals. As shown in Figure 6 of Exhibit B, rats implanted with conventionally cultured RCSN-3 cells showed a steady decrease in rotations, leveling off at 75% of the initial rotation values after approximately 12-16 weeks post-implant. In contrast, when obtained from the cell culture of the invention described in Example 1 of the subject application, RCSN-3 cells reached a plateau significantly sooner, at approximately 6 weeks post-implant. The comparative data demonstrate that the cell culture of the invention is particularly advantageous for cell transplantation. As indicated by Dr. Caviedes in his Declaration, "this improvement in apomorphine-induced circling behavior would be considered significant and unexpected by those of ordinary skill in the art."

It is well settled in patent law that "a greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue" *In re Corkill*, 226 USPQ 1005 (Fed. Cir. 1985). The benefits of the claimed cell culture are unexpected in view of the prior art, and have a significant, practical advantage. Therefore, the applicants respectfully submit that the cell culture of the invention is not obvious over the cited references. Accordingly, in view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachments: Request for Continued Examination
Petition and Fee for Extension of Time
Amendment Transmittal Letter
Declaration under 37 C.F.R. §1.132 by Dr. Caviedes with Exhibits A-C
Information Disclosure Statement; Form PTO/SB/08; copies of cited references
Iancu R. *et al.*, *Behavioral Brain Research*, 2005, 162:1-10
Nishimura, F. *et al.*, *Stem Cells*, 2003, 21:171-180
Bjorklund L.M. *et al.*, *PNAS*, 2002, 99(4):2344-2349
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Mukhida K. *et al.*, *Journal of Neuroscience*, 2001, 21(10):3521-3530
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